embodiments of the present invention may be used to treat radiation exposure that results from radiation therapy (*e.g.*, gamma rays from Co^{60}), a radiation attack, or a nuclear accident. Radiation from these sources includes x-ray, gamma ray, alpha, and beta radiation. Further information about the types of radiation emitted by these radiation sources can be found in the attached portion of a Department of Energy Report, which is posted on the Internet at http://tis.eh.doe.gov/ohre/roadmap/achre/intro_9_1.html.

Claim 2 has been amended to list the useful compounds that inhibit at least one of cell differentiation and cell proliferation. The amendment is supported by the original disclosure at line 17 of page 3 to line 7 of page 6 of the specification.

Claim 3 has been amended to more specifically list the compounds that inhibit at least one of cell differentiation and cell proliferation. The amendment to claim 3 is also supported at line 17 of page 3 to line 7 of page 6 of the specification. The phrase "Structurally similar derivatives thereof which exhibit antioxidant activity" has been deleted from claim 4. Claims 5 and 7 have been amended to render their terminology consistent with the terminology of amended claim 1. The word "substantially" has been deleted from claim 6. No new matter has been added by any of these amendments.

35 U.S.C. §112 rejections

In the Office Action, claims 1-4 and 6-10 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner considered the phrases "one or more compounds that regulate at least one of cell differentiation and cell proliferation" in claim 1; "vitamin D_3 analogs" in claim 2; "vitamin D_3 derivatives which regulate at least one of cell differentiation and cell proliferation" in claim 3; and "structurally similar derivatives [of the recited antioxidants] which exhibit antioxidant activity" in claim 4; not to be enabled by the specification. Specifically, the Examiner has taken the position that the present claims are wholly functional stating that applicant's claims (1) neither provide the elements required to practice the invention, nor (2) inform the public during the life of the patent of the limits of the invention. These rejections, at least insofar as they apply to the pending claims, as amended, are respectfully traversed for the reasons that follow.

Although the applicant does not agree with the Examiner's position, claims 1-4 have been amended to eliminate the phrases (1) "vitamin D_3 analogs," (2) "vitamin D_3 derivative which regulate at least one of cell differentiation and cell proliferation," and (3) "structurally similar derivatives thereof which exhibit antioxidant activity," in order to obviate the Examiner's rejections based on these phrases. Withdrawal of the rejections based on these phrases is respectfully requested.

Finally, the applicant has amended the phrase, "one or more compounds that regulate at least one of cell differentiation and cell proliferation" to replace the word "regulate" with the word "inhibit" in order to clarify this claim limitation. This phrase, as amended, is considered to be in compliance with 35 U.S.C. §112 for the reasons given below.

Referring first to the rules and laws governing the use of functional language in claims, MPEP § 2173.05(g) states as follows:

> A functional limitation is an attempt to define something by what it does, rather than by what it is (e.g., as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971).

With regards to enablement, MPEP §2164.08 states as follows:

> All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are analyzed individually...
>
> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention with 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)....[T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process

such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

Now referring to claim 1, claim 1 recites a method of treating radiation dermatitis caused by at least one type of radiation selected from alpha, beta, gamma-ray and x-ray radiation. This is the point of novelty of claim 1, namely, that applicant has found that by administering a topical composition containing one or more compounds that inhibit at least one of cell differentiation and cell proliferation, metabolites thereof, and pharmaceutically acceptable salts thereof; and one or more antioxidants, formulated in a topical carrier, effective relief of radiation dermatitis can be achieved. Thus, if the present claim were written in purely functional terms as the Examiner suggests, claim 1 would read as follows:

> A method for the prevention, reduction or treatment of radiation dermatitis comprising the step of administering an amount of a composition that is effective to prevent, reduce or treat radiation dermatitis.

From this it is immediately clear that the claims of the present application are not of the type which were present in either General Electric Company v. Wabash Appliance Corporation et al., 37 USPQ 466, 469 (US 1938) or University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1406 (CAFC 1997).

Rather, claim 1 is directed towards a method of treating radiation dermatitis using (1) a topical composition, which includes a combination of at least two compounds formulated in a pharmaceutically acceptable topical carrier. The point of novelty of the invention, as claimed in claim 1, is not the compounds *per se*, since each of the individual compounds used in the method of the present invention are known compounds. Thus, the present claims are exactly the type, which were approved in *In re Swinehart, supra*, namely, claims that define some part of the invention in functional terms.

In this case, the present invention defines the individual compounds present in the topical composition and the amounts used in functional terms since otherwise the applicant would not be able to obtain adequate protection for the full scope of the invention. The invention is the use of a combination of antioxidants and compounds that inhibit cell proliferation and/or cell differentiation as a combination in a topical composition to treat radiation dermatitis. If the applicant were required to list all compounds of these two classes, this would leave open opportunities for potential infringers to avoid the patent by simply making minor chemical

alterations to one of the listed compounds to create a new compound that still has the desired antioxidant activity or activity of inhibiting cell proliferation and/or cell differentiation. As a result, the only way that the applicant can adequately protect the present invention is to claim certain parts of the invention in functional terms in accordance with *In re Swinehart, supra.*

The specification illustrates how to prepare the topical composition of the present invention and how to use the topical composition to treat radiation dermatitis. To carry out the invention, a skilled person simply chooses one or more compounds that inhibit at least one of cell differentiation and cell proliferation, one or more antioxidants, and a pharmaceutically acceptable carrier for a topical composition and formulates them as described in the specification. Once the formulation is obtained, the skilled person need only follow the teachings of the specification to use the topical composition according to the method of claim 1 in order to treat radiation dermatitis.

The skilled person can either choose a compound that is known to inhibit at least one of cell differentiation and cell proliferation, or choose a compound and verify that it inhibits at least one of cell differentiation and cell proliferation by using a simple test. There are many tests known to a skilled person in the art that can be used to determine if a particular compound inhibits cell differentiation and/or cell proliferation. For example, the University of Massachusetts is offering a license for its method of screening for cancer drugs and other drugs that inhibit or promote cell growth, cell death or cell differentiation for diseases involving Erb action. See the webpage printout enclosed herewith having a URL of http://atlas.pharmalicensing.com/licensing/displicopp/548. In addition, DiscoveRx Corporation of Fremont, CA markets a Hithunter™ tyrosine kinase assay to detect inhibitors of tyrosine kinase and tyrosine phosphatase, which control or regulate cellular growth, proliferation and differentiation using ß-galactosidase EFC activity. See the attached article from DiscoveRx Corporation discussing the method of detecting compounds that control or regulate cellular growth, proliferation and differentiation.

Moreover, antioxidants are a well-known class of materials and persons skilled in the art know whether a material is an antioxidant and can routinely determine the appropriate amount of a particular material to be employed in order to obtain antioxidant activity. Simple tests can be employed to measure antioxidant activity. Thus, the disclosure is enabling for the antioxidants for these reasons.

Furthermore MPEP §2164.01(a) further states:

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
>
> *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). In *Wands*, the Court ...held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407.
>
> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.
>
> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The Office Action does not indicate that all of the factors listed above were considered in regard to this rejection based on nonenablement. It is applicants position that in view of the high level of skill in the art as demonstrated by the above mentioned facts, evidence and arguments,

the skilled person is capable of making and using the present invention based on the disclosure in the present specification and his common general knowledge.

Finally, the present claims are similar to those that were approved in *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971), cited by MPEP §2173.05(g), where it was held that the limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent" although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought. The limitations of the present claims, although functional, are also perfectly acceptable because they set definite boundaries on the patent protection sought because there are routine tests available to determine if a compound meets the functional definitions set forth in the claims. In this regard, the applicant amended all of the pending claims to change "regulates" to "inhibits" in order to improve the claims since the routine tests mentioned above are designed to determine whether a particular compound "inhibits" cell proliferation or cell differentiation. Accordingly, claim 1, as amended, is enabled and withdrawal of the rejection to claim 1 under 35 U.S.C. §112, first paragraph is respectfully requested.

Claims 4 and 6 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner considered the phrase "structurally similar" in claim 4, and the word "substantially" in claim 6 to be indefinite. Even though Applicant does not agree with the Examiner's position on these issues, Applicant has amended claims 4 and 6 by deleting "structurally similar" and "substantially" in order to obviate these rejections. Withdrawal of the rejections is respectfully requested.

35 U.S.C. § 103(a) Rejections

Claims 1-4, 6, 7 and 9 have been rejected under 35 U.S.C. §103 (a) as being unpatentable over Kita (WO 97/18817) and Sine et al. (US Patent No. 5,972,359) in view of "Sports Medicine Articles" from http://www.rehabnet.com/sports/actinic%20dermatitis.htm. This rejection is respectfully traversed and reconsideration is requested for the reasons, which follow.

Claim 1 has been amended to require applying the composition to an area of skin exposed or to be exposed to one or more types of radiation, selected from alpha, beta, gamma ray and x-ray radiation. The purpose of this amendment is to more clearly bring out the feature of the

present invention that it is designed to treat "radiation dermatitis." Radiation dermatitis is considered to be a serious, irreversible injury, which results primarily from exposure of the skin to high-energy ionizing radiation such as alpha, beta, gamma and x-ray radiation. See the enclosed publication "What is Ionizing Radiation" (6 pages) taken from http://tis.eh.doe.gov/ohre/roadmap/achre/into_9_1.html. Ionizing radiation is defined therein as any form of radiation that has enough energy to knock electrons out of atoms or molecules, creating ions. See page 2 of "What is Ionizing Radiation."

Ionizing radiation is thus distinguishable from, for example, actinic radiation, i.e. ultraviolet or violet radiation since ionizing radiation has significantly more energy than actinic radiation. Actinic radiation also does not have sufficient energy to knock electrons out of atoms or molecules creating ions. As a result, some types of damage to the skin caused by ionizing radiation, i.e. radiation dermatitis, is a different kind of damage than is caused by exposure of the skin to relatively lower energy actinic radiation such as ultraviolet radiation.

The article "Sunburn" by James Foster, MD, MS, of the Alverado Hospital Medical Center (12 pages) found at http://www.emedicine.com/EMERG/topic798.htm points out on page 1 of 12 that the most common deleterious effect of exposure to ultraviolet radiation is sunburn or solar erythema. This article also points out that long-term sun exposure may lead to the development of cancers such as basal cell carcinoma, squamous cell carcinoma and malignant melanoma. See page 2 of 12 of "Sunburn." These are the types of injury caused by exposure to the relatively lower energy ultraviolet or actinic radiation.

The article, "Radiation Safety Answers, Answer to Question #13," by Aggie Barlow, Radiation Safety Officer, Yale University (4 pages) found at http://www.yale.edu/oehs/rdsfq13.htm discusses the harmful effects of one type of higher energy ionizing radiation, namely, x-ray radiation. X-ray radiation has approximately 1000 times the energy of ultraviolet radiation since the wavelength of x-ray radiation is approximately 1000 times shorter than the wavelength of ultraviolet radiation and energy is inversely proportional to the wavelength of the radiation. The article "Radiation Safety Answers" discusses three types of biological effects of intense x-ray beams on pages 2-3 of the article: (1) reversible changes, (2) conditional reversible changes, and (3) irreversible changes. Among the reversible changes caused by x-ray radiation is erythema, similar to the most common injury caused by exposure to ultraviolet radiation, namely, solar erythema, as discussed above. See page 2 of "Radiation

Safety Answers." Among the irreversible changes caused by x-ray radiation is radiation cancer, again similar to the long-term effect of ultraviolet radiation of causing certain types of cancer as mentioned above.

However, a third, totally different type of injury caused by x-ray radiation, also considered irreversible, is radiation dermatitis, and, a fourth, totally different type of injury caused by x-ray radiation is chronic radiation dermatitis. See page 3 of "Radiation Safety Answers." Thus, "Radiation Safety Answers" makes it clear that (1) radiation dermatitis is a different injury than erythema and radiation cancer, and that (2) that ionizing x-ray radiation can cause radiation dermatitis. Exposure to ultraviolet radiation generally does not cause the irreversible damage associated with radiation dermatitis, such as permanent destruction of hair or sweat glands or of skin cells.

Accordingly, from the above publications it can be concluded that radiation dermatitis is a known illness, which is considered irreversible, and which is different than the damage that is caused by exposure to ultraviolet radiation. It can also be concluded that the mechanism causing radiation dermatitis is most likely associated with the knocking out of electrons from, for example, skin cells or elements thereof due to exposure to high-energy ionizing radiation, which phenomena does not occur as a result of exposure to the significantly lower energy ultraviolet radiation.

Therefore, it is considered that the present amendment, limiting the claims to treatment of radiation dermatitis caused by ionizing radiation, clearly distinguishes the present invention from all of the prior art relied upon by the Examiner since ionizing radiation causes a different, more harmful type of damage, characterized as "radiation dermatitis," than does ultraviolet radiation due to its higher energy state. Thus, a skilled person would not apply the teachings of prior art relating to the treatment of sunburn to the treatment of radiation dermatitis which results from exposure to alpha, beta, gamma or x-ray radiation, as claimed, since it is apparent from, for example, "Radiation Safety Answers" that radiation dermatitis caused by these types of high-energy radiation is a different type of injury than the types of injury that is typically caused by exposure to the relatively lower energy ultraviolet radiation. Accordingly, all claims of the present application are considered to be patentable over the cited prior art for at least this reason.

Kita discloses an ophthalmic or dermatological composition comprising vitamin D for treating disturbed metabolism in eye tissues and protecting skin against UV radiation. However,

Kita does not teach the use of the composition for treating radiation dermatitis or radiation injury. In fact, Kita disavows treatment of radiation damage to the skin when it states that "[I]n U.S. Pat. No 4,610,978, Dikstein et al disclose active vitamin D as a skin cream for treating the skin. By contrast, the present invention is a cosmetic or other dermatological composition which uses vitamin D to protect the skin against UV radiation."

Sine et al. discloses a composition for regulating a skin condition comprising a particulate material such as TiO_2 (col. 4, lines 41-42 of Sine et al) and a carrier containing vitamin E acetate, vitamin A, D-panthenol, acrylic copolymer and PEG stearate (col. 5, line 53 of Sine et al.). According to Sine et al., regulating a skin condition includes regulating visible and/or tactile discontinuities in skin, including but not limited to visible and/or tactile discontinuities in skin texture and/or color, more especially discontinuities associated with skin aging. Such discontinuities may be induced or caused by internal and/or external factors. Extrinsic factors include ultraviolet radiation (e.g., from sun exposure), environmental pollution, wind, heat, low humidity, harsh surfactants, abrasives, and the like. Intrinsic factors include chronological aging and other biochemical changes from within the skin." (Col. 3, lines 25-36). Nowhere does Sine et al. teach using the composition to treat radiation dermatitis. Rather, Sine et al. relates again to a purely cosmetic composition for the skin. Sine et al. is mainly concerned with "masking" the skin discontinuity caused by aging, UV radiation, wind, pollution, heat, low humidity, and harsh surfactant among many other factors.

The composition of Sine et al. is used to impart an essentially immediate visual improvement in skin appearance (col. 2, lines 29-32 of Sine et al.). The compositions of Sine et al. are characterized by their contrast ratio and % transmittance or coverage index (col. 2, lines 32-34 of Sine et al.). In fact, Sine et al. goes extra length to discuss the importance of refractive index of the particulate material. Clearly, UV radiation is just one of the more than 10 factors that can cause such skin discontinuities. Furthermore, Sine et al. even admits that "it is believed that this acute skin appearance improvement results at least in part from therapeutic coverage or masking of skin imperfections by the particulate material." (Col. 3, lines 19-23 of Sine et al.)

Furthermore, the combination of the teachings of Kita and Sine et al. would result a composition unsuitable for the objective of Kita. Kita uses its composition for ophthalmic treatment. Clearly, the TiO_2 particulates contained in the composition of Sine et al. would result in a composition unsuitable to be used in ophthalmic treatment since such particulates would

cause abrasive damage to the eyeball. Therefore, a skilled person reading these two references would not be motivated to combine the teachings of these two references.

"Sports Medicine Articles" discloses that actinic (radiation) dermatitis may result from exposure of skin to UV radiation from the sun. However, it is clear that not all persons exposed to UV radiation will get radiation dermatitis. Importantly, neither Kita nor Sine et al. teaches or suggests the use of its composition for the treatment of radiation dermatitis. In fact, a skilled person would be led away from applying the primarily cosmetic compound of Sine et al. to an area of the skin affected with radiation dermatitis since there is no teaching or suggestion in Sine et al. which would lead a skilled person to expect any beneficial result whatsoever from using the composition of Sine et al. to treat radiation dermatitis. "Sports Medicine Articles" merely teaches the fact there is a skin condition called radiation dermatitis that MAY be caused by a prolonged exposure to the sun. The only remedies suggested by Sports Medicine Articles is to use a sunscreen, wear clothing, or apply aloe vera, cortico-steroids or anti-inflammatory drugs. The composition of Sine et al. does not fall into any of these categories.

All of the other rejected claims 3-4, 6, 7 and 9 depend from claim 1. Accordingly these claims are considered to be patentable for at least the same reasons given above with respect to claim 1. Withdrawal of the rejection is respectfully requested.

Claims 5, 8, 10 and 11 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kita (WO 97/18817-U.S. Patent No. 6,162,801 is used herein as an English Translation) and Sine et al. (U.S. Patent No. 5,972,359) in view of "Sports Medicine Articles" (above) and further in view of Neigut (U.S. Patent No. 6,048,886), Schonrock et al. (U.S. 5,876,737), and Gers-Barlag et al. (U.S. Patent No. 5,952,391).

Applicant refers to the facts, evidence and arguments discussed above with regards to claim 1 and considers that at least claims 5, 8 and 10 are considered patentable for the same reasons as claim 1 since claims 4, 8 and 10 depend from claim 1.

Neigut discloses a composition comprising vitamins A, D, E, ascorbyl palmitate, α-lipoic acid, and an antioxidant enzyme, superoxide dismutase, in a corn oil vehicle, and a method of treating skin conditions such as psoriasis (see col. 1, lines 18-19, and col. 7, lines 40-60 of Neigut). Applicant wants to further point out that Neigut uses vitamin D without mentioning which vitamin D it refers to. There are several forms of vitamin D and thus it is not clear that the vitamin D in Neigut is, in fact, vitamin D_3.

Schonrock et al. uses a composition including vitamin E acetate and hydroxypropylmethylcellulose for cosmetic and topical dermatological treatment (col. 14, lines 1-45, col. 1, lines 6-9 of Schonrock et al.).

Gers-Barlag et al. discloses the use of quercetin against UV-induced decomposition of dibenzoylmethane and its derivatives (col. 4, lines 45-61, and col. 14, lines 25-40 of Gers-Barlag).

First of all, the combination of all the above references still lacks an element, treating radiation dermatitis caused by one or more radiations selected from the group consisting of alpha, beta, gamma-ray and x-ray radiations, which is required by claims 5, 8 and 10.

In addition, the composition as claimed in claim 11 of the present invention achieve an unexpected result by combining the ingredients of one or more compounds that inhibit cell differentiation and/or cell proliferation and one or more antioxidant in a pharmaceutically acceptable carrier. Namely, the composition of the present invention is surprisingly capable of treating radiation dermatitis caused by alpha, beta, gamma ray and/or x-ray radiation. In fact, the composition of claim 11 is exemplified in the examples of the present application. Thus, even if the Examiner has made out a *prima facie* case of obviousness, it is rebutted by the significant unexpected result that the applicant has demonstrated for the specific composition of claim 11.

Furthermore, the skilled person would not combine some of the references as the Examiner suggests. For example, one reading Gers-Berlag would have no motivation to add quercetin to the composition of, e.g. Neigut, or Kita, since the compositions of Neigut and Kita doe not contain dibenzoylmethane, for which quercetin functions as a protecting agent according to Gers-Berlag (col. 7, line 62 to col. 8, lines 67 of Gers-Barlag). Thus, if the composition does not contain dibenzoylmethane, there is no reason to add quercetin as taught by Gers-Berlag.

The skilled person would also not combine Sine et al. with the other references, as discussed above, since Sine et al. is primarily concerned with "hiding" skin imperfections by choosing ingredients with proper reflectivity index (col. 1, line 10-13, col. 2, lines 23-26 of Sine et al.). As discussed above, for example, a proposed combination of Kita and Sine et al. would be a problem since TiO_2 is not compatible with an ophthalmic composition.

Finally, the Examiner has picked and chosen specific ingredients from different compositions disclosed for use for different purposes from not less than six references to arrive at a rejection of the composition of claim 11. It is only with the use of hindsight that these six

specific ingredients from these six references can be chosen. For example, to arrive at the invention as claimed in claim 11 from Neigut, considered to be the closest of the six references to the composition of claim 11), a skilled person has to:

1) choose vitamin D_3 out of all the possible vitamin D's;

2) add quercetin to the composition even though it does not contain dibenzoylmethane type material;

3) use a dispersion of vitamin A and D_3;

4) use vitamin E acetate instead of vitamin E; and

4) determine the specific amounts for each of vitamin A, vitamin D_3, vitamin E acetate, ascorbyl palmitate, quercetin, α-lipoic acid to be used in the particular composition.

Clearly, the skilled person would not arrive at the specific composition of claim 11 of the present application due to the teachings mentioned above and the necessity of making so many modifications to the cited prior art composition. Therefore, claim 11 is considered to be patentable over the cited references for this additional reason.

For the foregoing reasons, claims 5, 8, 10 and 11 are considered to be patentable in view of Kita, Sine et al., "Sports Medicine Articles," Neigut, Schonrock et al., and Gers-Barlag et al. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

In view of the foregoing remarks, Applicant respectfully submits that all of the pending claims are in condition for allowance and respectfully requests a favorable Office Action so indicating.

Respectfully submitted,

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Redline Version of Claims Showing Amendments

1. (Amended) A method for the prevention, reduction or treatment of radiation dermatitis caused by one or more types of radiation selected from the group consisting of alpha radiation, beta radiation, gamma ray radiation and x-ray radiation, comprising the step of applying to an area of skin which has been or will be exposed to said one or more types of radiation, a topical composition which comprises:

-an amount of one or more compounds that ~~regulate~~ inhibit at least one of cell differentiation and cell proliferation, metabolites thereof, and pharmaceutically acceptable salts thereof, which is effective, when administered topically in the topical composition to inhibit at least one of cell differentiation and cell proliferation, and

an effective amount of one or more antioxidants, and pharmaceutically acceptable salts thereof,

formulated in a pharmaceutically acceptable carrier for a topical composition.

2. (Amended) A method as claimed in claim 1, wherein the one or more compounds that ~~regulate~~inhibit at least one of cell differentiation and cell proliferation ~~is~~are selected from the group consisting of vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, compounds that are converted or metabolized into vitamin D_3 in the human body, metabolites thereof, and pharmaceutically acceptable salts thereof~~vitamin D_3, vitamin D_3 analogs and metabolites thereof~~.

3. (Amended) A method as claimed in claim 1, wherein the one or more compounds that ~~regulate~~inhibit at least one of cell differentiation and cell proliferation are selected from the group consisting of: cholesterols, 7-dehydrocholestrol, vitamin D_3, 1, 25-dihydroxyvitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and 25-hydroxycholecalciferol, calcitriol~~vitamin D_3, 1, 25-dihydroxyvitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and other~~

~~vitamin D_3 derivatives which regulate at least one of cell differentiation and cell proliferation~~, and pharmaceutically acceptable salts thereof.

4. (Amended) A method as claimed in claim 1, wherein the one or more antioxidants are selected from the group consisting of: ascorbyl palmitate, ascorbic acid, vitamin A, vitamin E acetate, α-lipoic acid, coenzyme Q10, glutathione, (-)-epigallocatechin-3-gallate, catechin, galangin, rutin, luteolin, morin, fisetin, silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, curcuminoid, ~~and structurally similar derivatives thereof which exhibit antioxidant activity,~~ and pharmaceutically acceptable salts thereof.

5. (Amended) A method as claimed in claim 1, wherein the compound that ~~regulates~~inhibits at least one of cell differentiation and cell proliferation comprises vitamin D_3, and the antioxidant comprises vitamin A, vitamin E acetate, and α-lipoic acid.

6. (Amended) A method as claimed in claim 1, wherein the pharmaceutically acceptable carrier comprises a sufficient amount of at least one non-U.S.P. hydrophilic ointment base to form a ~~substantially~~ topical composition.

7. (Amended) A method as claimed in claim 6, wherein the pharmaceutically acceptable carrier further comprises a sufficient amount of a panthenol selected from D-panthenol and DL-panthenol to promote penetration of one or more of the antioxidants and compounds which ~~regulate~~inhibit at least one of cell differentiation and cell proliferation, into the skin.

DOE Openness: Human Radiation Experiments:
Roadmap to the Project

ACHRE Report

What Is Ionizing Radiation?

What is *radiation*?

Radiation is a very general term, used to describe any process that transmits energy through space or a material away from a source. Light, sound, and radio waves are all examples of radiation. When most people think of radiation, however, they are thinking of *ionizing radiation*--radiation that can disrupt the atoms and molecules within the body. While scientists think of these emissions in highly mathematical terms, they can be visualized either as subatomic particles or as rays. Radiation's effects on humans can best be understood by first examining the effect of radiation on *atoms*, the basic building blocks of matter.

What is *ionization*?

Atoms consist of comparatively large particles (protons and neutrons) sitting in a central nucleus, orbited by smaller particles (electrons): a miniature solar system. Normally, the number of protons in the center of the atom equals the number of electrons in

orbit. An *ion* is any atom or molecule that does not have the normal number of electrons. *Ionizing radiation* is any form of radiation that has enough energy to knock electrons out of atoms or molecules, creating ions.

How is ionizing radiation measured?

Measurement lies at the heart of modern science, but a number by itself conveys no information. Useful measurement requires both an instrument for measurement (such as a stick to mark off length) and an agreement on the *units* to be used (such as inches, meters, or miles). The units chosen will vary with the *purpose* of the measurement. For example, a cook will measure butter in terms of tablespoons to ensure the meal tastes good, while a nutritionist may be more concerned with measuring calories, to determine the effect on the diner's health.

The variety of units used to measure radiation and radioactivity at times confuses even scientists, if they do not use them every day. It may be helpful to keep in mind the *purpose* of various units. There are two basic reasons to measure radiation: the study of physics and the study of the biological effects of radiation. What creates the complexity is that our instruments measure *physical* effects, while what is of interest to some are *biological* effects. A further complication is that units, as

with words in any language, may fade from use and be replaced by new units.

Radiation is not a series of distinct events, like radioactive decays, which can be counted individually. Measuring radiation in bulk is like measuring the movement of sand in an hourglass; it is more useful to think of it as a continuous flow, rather than a series of separate events. The *intensity* of a beam of ionizing radiation is measured by counting up how many ions (how much electrical charge) it creates in air. The *roentgen* (named after Wilhelm Roentgen, the discoverer of x rays) is the unit that measures the ability of x rays to ionize air; it is a unit of exposure that can be measured directly. Shortly after World War II, a common unit of measurement was the *roentgen equivalent physical (rep)*, which denoted an ability of other forms of radiation to create as many ions in air as a roentgen of x rays. It is no longer used, but appears in many of the documents examined by the Advisory Committee.

What are the basic types of ionizing radiation?

There are many types of ionizing radiation, but the most familiar are *alpha*, *beta*, and *gamma/x-ray* radiation. *Neutrons*, when expelled from atomic nuclei and traveling as a form of radiation, can also be a significant health concern.

How Do Scientists Determine the Long-Term Risks from Radiation?

Alpha particles are clusters of two neutrons and two protons each. They are identical to the nuclei of atoms of helium, the second lightest and second most common element in the universe, after hydrogen. Compared with other forms of radiation, though, these are very heavy particles--about 7,300 times the mass of an electron. As they travel along, these large and heavy particles frequently interact with the electrons of atoms, rapidly losing their energy. They cannot even penetrate a piece of paper or the layer of dead cells at the surface of our skin. But if released within the body from a radioactive atom inside or near a cell, alpha particles can do great damage as they ionize atoms, disrupting living cells. Radium and plutonium are two examples of alpha emitters.

Beta particles are electrons traveling at very high energies. If alpha particles can be thought of as large and slow bowling balls, beta particles can be visualized as golf balls on the driving range. They travel farther than alpha particles and, depending on their energy, may do as much damage. For example, beta particles in fallout can cause severe burns to the skin, known as beta burns. Radiosotopes that emit beta particles are present in fission products produced in nuclear reactors and nuclear explosions. Some beta-emitting radioisotopes, such as iodine 131, are administered internally to patients to diagnose and treat disease.

Gamma and *x-ray* radiation consists of packets of energy known as *photons*. Photons have no mass or charge, and they travel in straight lines. The visible light seen by our eyes is also

made up of photons, but at lower energies. The energy of a gamma ray is typically greater than 100 kiloelectron volts (keV--"k" is the abbreviation for *kilo*, a prefix that multiplies a basic unit by 1,000) per photon, more than 200,000 times the energy of visible light (0.5 eV). If alpha particles are visualized as bowling balls and beta particles as golf balls, photons of gamma and x-radiation are like weightless bullets moving at the speed of light. Photons are classified according to their origin. Gamma rays originate from events within an atomic nucleus; their energy and rate of production depend on the radioactive decay process of the radionuclide that is their source. X rays are photons that usually originate from energy transitions of the electrons of an atom. These can be artificially generated by bombarding appropriate atoms with high-energy electrons, as in the classic x-ray tube. Because x rays are produced artificially by a stream of electrons, their rate of output and energy can be controlled by adjusting the energy and amount of the electrons themselves. Both x rays and gamma rays can penetrate deeply into the human body. How deeply they penetrate depends on their energy; higher energy results in deeper penetration into the body. A 1 MeV ("M" is the abbreviation for *mega*, a prefix that multiplies a basic unit by 1,000,000) gamma ray, with an energy 2,000,000 times that of visible light, can pass completely through the body, creating tens of thousands of ions as it does.

A final form of radiation of concern is *neutron* radiation. Neutrons, along with protons, are one of the components of the atomic nucleus.

Like protons, they have a large mass; unlike protons, they have no electric charge, allowing them to slip more easily between atoms. Like a Stealth fighter, high-energy neutrons can travel farther into the body, past the protective outer layer of the skin, before delivering their energy and causing ionization.

Several other types of high-energy particles are also ionizing radiation. Cosmic radiation that penetrates the Earth's atmosphere from space consists mainly of protons, alpha particles, and heavier atomic nuclei. Positrons, mesons, pions, and other exotic particles can also be ionizing radiation.

09/99 3003

Part #5

BIOSCIENCE VALUATION

pharmalicensing

Friday, 8 March 2002

Drug Screening Method for Estrogen Receptor Beta (ERb) Modulators

Commercial Ventures & Intellectual Property - University of Massachusetts

Screening for cancer drugs and other drugs that inhibit or promote cell growth, cell death or cell differentiation for diseases involving ERb action

licensing contact

David Warshawsky *Licensing Associate*

development status

Preclinical

industry sectors

Biotechnology
Biotechnology: High throughput screening
Biotechnology: Assay systems
Diagnostic
Diagnostic: Test systems

therapeutic targets

Oncology
Oncology: Cytostatic
Cardiovascular
Cardiovascular: Cardiac therapy
Central Nervous System
Central Nervous System: Other CNS
Musculoskeletal
Musculoskeletal: Other musculoskeletal

full description

ER-beta mediates the action of estrogen/antiestrogen/estrogen mimics in a great variety of normal and malignant tissues.

Its action is mediated via a signaling pathway that up-regulates or down-regulates specific genes (ER-beta-regulated genes).

The effect of any compound on ER-beta regulated cell growth/cell death/cell cycle arrest can be determined by adding the compound to culture cells expressing the receptor and measuring alteration in expression levels of ER-beta regulated genes.

In addition, the activation of ER-beta action can also be measured directly by using reporter systems constructed from regulatory sequences of the ER-beta-regulated genes.

Application:

Screening for cancer drugs and other drugs that inhibit or promote cell growth, cell death or cell differentiation for diseases involving ERb action, including prostate, breast and ovarian cancer, neurological disorders, osteoporosis and cardiovascular disease.

Advantage:

This method enables simple and rapid screening of large numbers of compounds. It has high specificity.

Importantly, it not only permits identification of agents interacting with ER-beta but also provides biological endpoints or "read-outs" such as cell death/apoptosis/growth inhibition.

Inventor: Shuk-mei Ho, Ph.D.

Licensing ref: UMMC 00-28

DiscoveRx

Homogeneous Assays for Tyrosine Kinase and Tyrosine Phosphatase Activity using β-Galactosidase Enzyme Fragment Complementation

Shahin Panah, Poonam Kaul, Hyna Fablonar, Riaz Rouhani, Richard M. Eglen

DiscoveRx Corporation, Fremont, CA

Abstract

Protein tyrosine kineses and phosphatases control several cellular responses including growth, proliferation and differentiation. We report a homogenous, non-isotopic assay using ß-galactosidase EFC to detect inhibitors of tyrosine kinase and tyrosine phosphatase activity. In this format, inactive fragments of galactosidase, enzyme acceptor (EA) and enzyme donor (ED) complement to form active enzyme. Binding of an ED-conjugated peptide to an antibody inhibits complementation, while unlabeled peptide displaces the ED-conjugate. This results in increased ß-galactosidase activity that is detected subsequently using either chemiluminescent or long wavelength fluorescent substrates.

HitHunter™ tyrosine kinase assay has been developed to measure activity of the human insulin receptor, EGF receptor kinase domains and Src (EC_{50} = 2.8 nM, 4.4 nM and 4.9 nM respectively). HitHunter™ tyrosine phosphatase activity was measured similarly using PTP 1B enzyme (EC_{50} = 48 nM). Assay performance characteristics (Z' = 0.5-0.7, CV = 5-8 %) and a simple two step addition protocol make it ideal for HTS.

Introduction

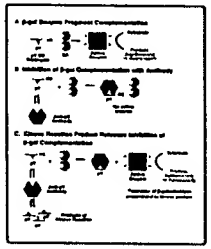
Tyrosine kinase (TK) plays a critical role in cellular signal transduction pathways involved in the regulation of many biological mechanisms. Protein phosphatase catalyzes the dephosphorylation of phosphoproteins, thus reversing the action of protein kinases. Protein phosphorylation and dephosphorylation are the basis for the regulation of many diverse cellular processes that include metabolism, cell division, differentiation and development. For this reason, tyrosine kinase and tyrosine phosphatase inhibitors are an important focus for new drug therapeutics.

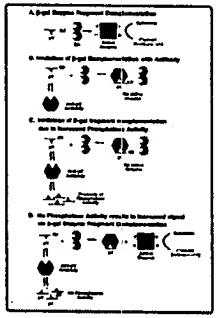
The HitHunter™EFC Tyrosine Kinase and Tyrosine Phosphatase assays are robust, reliable assay platforms designed specifically for high-throughput screening. The EFC assay platform provides a rapid and homogeneous methodology for the detection of protein phosphorylation and dephosphorylation of tyrosine during the cell signaling process. The HitHunter™EFC platform features the flexibility needed for high throughput screening with the following assay characteristics:

- Homogeneous
- Single well assay
- Single, biological label
- Miniaturizable (96/384/1536 formats)
- Luminescence or Fluorescence readouts
- Easily automated

HitHunter™ Enzyme Fragment Complementation

Enzyme Fragment Complementation Technology (EFC) is based on recombinant DNA techniques to genetically engineer ß-galactosidase into two inactive fragments - Enzyme Acceptor (EA) and Enzyme Donor (ED). These fragments can recombine spontaneously to form active ß-galactosidase by a process called complementation. The active tetrameric ß-galactosidase can be measured by hydrolysis of fluorogenic or luminescent substrates. Attachment of a ligand to ED does not affect complementation, but subsequent binding of a receptor or binding protein will inhibit enzyme formation.





A Incubation of ED-pY conjugate with EA (Enzyme Acceptor) results in formation of active, tetramer ß-galactosidase, which can be measured by hydrolysis of fluorogenic or luminescent substrates.

B Binding of anti-phosphotyrosine antibody to the ED-pY conjugate prevents formation of active enzyme.

C In the presence of kinase reaction products, competition for binding sites leads to an increase of free ED-pY ligand conjugate, which complements with EA to form active enzyme. Active enzyme hydrolyzes the substrate for readout either by luminescence or fluorescence. The amount of enzyme activity is directly proportional to the concentration of the kinase products and its relative affinity for the kinase substrate.

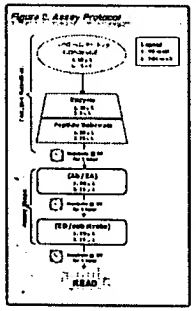
A Same as HitHunter™ EFC assay principle.

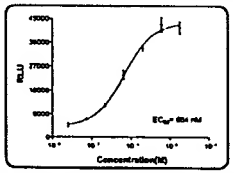
B Same as HitHunter™ EFC assay principle.

C Dephosphorylation of phosphotyrosines increases phosphatase products, leading to an increase of free ED-pY ligand conjugate. Binding of anti-phosphotyrosine antibody to ED-pY prevents formations of active enzyme. Lack of signal indicates increased phosphatase activity.

D In the presence of no phosphatase activity, phosphorylated tyrosines compete for binding sites. Thus, there is an increase in the amount of free ED-pY ligand conjugate, which complements with EA to form active enzyme. Active enzyme hydrolyzes the substrate for readout either by luminescence or fluorescence. The amount of enzyme activity is directly proportional to the concentration of the lack of phosphatase activity.

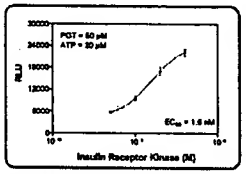
HitHunter™ EFC TK in a 384-well format



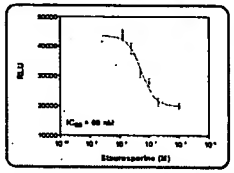


Tyrosine Kinase standard ranges from 0 to 18 µM in the 384-well assay. The standard curve illustretes a positive reading from low to high levels of phosphotyrosine.

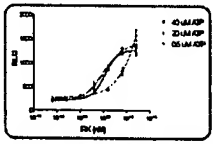
Z' factor	0.69
Signal to Noise Ratio	18
EC_{50}	0.66 µM/well



A concentration response curve for insulin receptor kinase enzyme was performed. The assay was initiated by the addition of ATP and PGT. The amount of phosphorylated peptide was quantitated after a two hour incubation at room temperature.

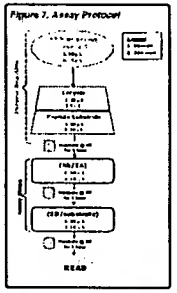


Staurosporine is a potent kinase inhibitor and was tested in the presence of IRK activity. HitHunter™ EFC Tyrosine Kinase Assay exhibited a dose dependent decrease in kinase activity in the presence of staurosporine.

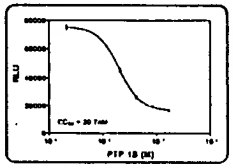


Inhibitors of tyrosine kinase are often ATP competitors. The IRK enzyme activity was measured in the presence of varying concentrations of ATP. The data exhibits the utility of HitHunter™ EFC Tyrosine Kinase Assay over an ATP concentration range of 0.5 to 40 µM.

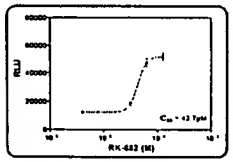
HitHunter™ EFC TP in a 384-well format



Z' factor	0.72
Signal to Noise Ratio	4
EC_{50} (µM well)	0.66



A concentration response curve for PTB 1B was performed under the established optimum conditions using PTB 1B substrate at 11.2 µM. The enzyme was tested at 2.1nM, 21 nM, 42 nM, 84 nM and 168 nM concentration.



RK-682 is a well known inhibitor of certain tyrosine phosphateses and was tested in the presence of PTB 1B activity. HitHunter™ EFC Tyrosine Phosphatase Assay exhibited a dose dependent decrease in phosphatase activity in the presence of RK-682.

Summary and Conclusion

SUMMARY

- HitHunter™ EFC assays for Tyrosine Kinase and Tyrosine Phosphatase have been demonstrated with both chemiluminescent and fluorescent substrates in a simple two step process that can be miniaturized in a 384 well plate format.
- Assay performance is excellent with Z' factor of 0.5-0.7 and CVs of 5-8%.
- Activity of human insulin receptor, EGF receptor kinase domains, and SRC can be measured with these assays.

CONCLUSION

The HitHunter™ EFC Tyrosine Kinase and Tyrosine Phosphatase Assays can detect phosphorylated and daphosphorylated tyrosines as a result of enzyme reactions with no wash / transfer steps and is assayed in the same well, making it highly suitable for HTS screening for kinase and phosphatase inhibitors.

Sunburn

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Editor's Email: James Li, MD

eMedicine Journal, August 21 2001, **Volume** 2, **Number** 8

INTRODUCTION

Background: Sunburn is an acute cutaneous inflammatory reaction that follows excessive exposure of the skin to ultraviolet radiation (UVR). Long-term adverse health effects of repeated exposure to UVR are well described but are beyond the scope of this article.

Pathophysiology: Exposure to solar radiation has the beneficial effects of stimulating the cutaneous synthesis of vitamin D and providing radiant warmth. Unfortunately, when the skin is subjected to excessive radiation in the ultraviolet range (wavelength <400 nm), deleterious effects may occur. The most common is acute sunburn or solar erythema.

Solar erythema is associated with microscopic changes in the skin, detectable within 30

minutes of exposure to UVR. The most characteristic changes include formation of epidermal sunburn cells, damaged keratinocytes with hyaline cytoplasm, and pyknotic nuclei. Epidermal Langerhans cell and mast cell numbers may decrease, while the relative percentage of hypogranulated or degranulated cells may increase. Superficial blood vessels show endothelial swelling, perivenular edema, and a mixed perivascular infiltrate.

The precise biochemical pathways that lead to the sunburn reaction are not well understood but appear to involve multiple inflammatory mediators, including histamine, prostaglandins, and cytokines.

Less intense or shorter-duration exposure to UVR results in an increase in skin pigmentation, known as tanning, which provides some protection against further UVR-induced damage. The increased skin pigmentation occurs in 2 phases, (1) immediate pigment darkening, and (2) delayed tanning. Immediate pigment darkening occurs during exposure to UVR and results from alteration of existing melanin (oxidation, redistribution). It may fade rapidly or persist for several days. Delayed tanning results from increased synthesis of epidermal melanin and requires a longer period of time to become visible (24-72 h). With repeated exposure to UVR, the skin thickens, primarily due to epidermal hyperplasia with thickening of the stratum corneum.

Frequency:

- **In the US:** Incidence is highest in areas with the highest flux of solar radiation (ie, the southern United States).
- **Internationally:** Incidence is increased in regions that are closer to the equator, that are higher in altitude, and where individuals have lighter baseline skin pigmentation.

Mortality/Morbidity:

- Uncomplicated sunburn is associated with minimal short-term morbidity. Most cases resolve spontaneously with no significant sequelae.
- In rare cases, sunburn may be so severe and diffuse that it results in second-degree burns, dehydration, secondary infection, shock, or even death.
- Morbidity and mortality associated with long-term sun exposure is related primarily to the development of cutaneous neoplasms, including basal cell carcinoma, squamous cell carcinoma, and malignant melanoma.

Race: Lighter-skinned individuals are affected more frequently and severely. Skin types may be divided into 6 categories, based on an individual's tendency to tan and/or burn (see Table 1).

Table 1. Skin Phototypes

Skin Phototype	Description	Typical Features	MED	Minimum SPF
	Always burns, never	White skin, blue/hazel	15-30	

I	tans	eyes, blond/red hair	mJ/cm^2	≥15
II	Always burns, tans minimally	Fair skin, blue eyes	25-40 mJ/cm^2	≥15
III	Burns minimally, tans slowly	Darker Caucasian skin	30-50 mJ/cm^2	10-15
IV	Burns minimally, tans well	Light brown skin, Mediterranean	40-60 mJ/cm^2	6-10
V	Rarely burns, tans profusely/darkly	Brown skin, Middle Eastern, Latin American	60-90 mJ/cm^2	4-6
VI	Never burns, always tans, deeply pigmented	Dark brown or black skin	90-150 mJ/cm^2	None

Age: Most people get the majority of their sun exposure when young, making sunburn more common in children and young adults. Some elderly individuals have a blunted sunburn response.

CLINICAL

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History:

- Recent sun exposure or outdoor activity; outdoor occupations or hobbies
- Erythema develops after 2-6 hours and peaks at 12-24 hours.
- Pain
- Possible fever, chills, malaise, nausea, or vomiting in severe cases
- Blistering
- Erythema that resolves over 4-7 days, usually with skin scaling and peeling
- Assess for exposure to photosensitizing drugs.

Physical:

- Patients at highest risk typically have fair skin, blue eyes, and red or blond hair.
- Immediate or early erythema occurs during UVR exposure and fades within 30 minutes.
- The acute inflammatory response is greatest 20-24 hours after exposure.
    - Erythema
    - Warmth

- Tenderness
- Edema
- Blistering (severe cases)

- Fever can present in severe cases.
- Most exposure is limited to sun-exposed areas of the body; however, significant transmission of UVR may occur through some clothing, resulting in sunburn on clothed skin.
- Delayed scaling and desquamation occurs 4-7 days after exposure.

Causes:

- The electromagnetic spectrum can be divided according to wavelength into ultraviolet (<400 nm), visible (400-760 nm), and infrared (>760 nm).
  - Sunburn is caused by excessive exposure of the skin to UVR.
  - The ultraviolet spectrum can be divided into ultraviolet A (UV-A), 320-400 nm; ultraviolet B (UV-B), 290-320 nm; and ultraviolet C (UV-C), 200-290 nm.
  - Solar UVR of wavelengths shorter than 290 nm is filtered out or absorbed in the outer atmosphere and is not encountered at sea level.
  - UV-B radiation is much more potent at inducing erythema than UV-A and is, therefore, the principal cause of sunburn (about 85%).
  - However, UV-A comprises the majority of UVR reaching the surface of the earth (about 90% at midday) and, therefore, accounts for a significant percentage of the immediate and long-term cutaneous effects of UVR.
- The minimal single dose of UVR (energy per unit area) required to produce erythema at an exposed site is known as the minimal erythema dose (MED). Moderate-to-severe sunburn occurs at 3-8 MEDs.
- Multiple factors influence UVR-induced erythema.
  - Wavelength: UV-B is more erythemogenic than UV-A. Multiple wavelengths may result in an additive effect.
  - Skin pigmentation: Compared with white-skinned individuals, moderately pigmented races require 3-5 times more UVR exposure to cause erythema; blacks require up to 30 times more. Facultative (induced) tanning increases MEDs by only 2-3 times.
  - Skin thickness

- Hydration: UVR penetrates moist skin more effectively than dry skin.
- Anatomic site: MEDs are greater on the limbs than on the face, neck, and trunk.
- Environmental reflection: Radiation is 80% reflected by snow and ice, compared to 20% by sand.
- Altitude: UVR increases 4% for every 300-m (1000-ft) increase in elevation.
- Latitude: Exposure is greater at lower latitudes.
- Time of day: 65% of UVR reaches the earth between 10 am and 2 pm.

DIFFERENTIALS

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Burns, Chemical
Burns, Thermal
Cellulitis
Dermatitis, Atopic
Dermatitis, Contact
Dermatitis, Exfoliative
[Heat Exhaustion and Heat Stroke]

Systemic Lupus Erythematosus

WORKUP

Section 5 of 10 [Back Top Next]

Lab Studies:

- None indicated for uncomplicated cases

Imaging Studies:

- None indicated for uncomplicated cases

Procedures:

- Skin biopsy may be useful if the diagnosis is in doubt or to exclude other diseases in the differential.

TREATMENT

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Prehospital Care:

- In most cases, prehospital care involves providing simple first aid to treat patient symptoms.

- In severe cases, patients may develop second-degree burns, which rarely require aggressive fluid resuscitation and skin care.

Emergency Department Care:

- Most sunburns, while painful, are not life threatening, and treatment is primarily symptomatic.
- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have antiprostaglandin effects and are useful to relieve pain and inflammation, especially when given early. Cool soaks with water or Burow solution also provide temporary relief.
- Systemic steroids may shorten the course and reduce the pain of sunburn when given early and in relatively high doses (equivalent to 40-60 mg/d of prednisone).
    - When used, prescribe them for only a few days, with no need for a taper.
    - In the presence of severe second-degree burns, steroids are best avoided because they increase the risk of infection.
    - Topical steroids show minimal, if any, benefit.
- Severe cases may require treatment of accompanying dehydration or secondary infection.
    - Severe cases may be associated with other heat-related illnesses, including heat exhaustion and heat stroke.
    - In rare cases, patients may require admission to a burn unit for aggressive skin care, intravenous fluids, and electrolyte management. Shock can occur.
- Prophylaxis of sunburn may be possible if a patient is treated with systemic steroids, equivalent to a daily dose of 60-80 mg of prednisone (1.0-1.5 mg/kg), prior to or shortly following sun exposure.

Consultations:

- Consult a dermatologist if the diagnosis of sunburn is in doubt or for children who appear to burn easily. In the latter case, a more serious underlying disorder may be present.
- Severe cases may require consultation with pediatricians or internists for hospital admission. Patients rarely require care in a dedicated burn unit.

MEDICATION

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Minor sunburn can be relieved to some extent with cool compresses or a cool bath. Administration of nonprescription analgesics and NSAIDs for the treatment of pain and inflammation is recommended.

Drug Category: *Analgesics* -- Pain control is essential to quality patient care. It ensures patient comfort and promotes pulmonary toilet. Most analgesics have sedating properties, which are beneficial for patients who have sustained sunburns.

Drug Name	Aspirin (Bayer, Anacin, Bufferin) -- Used for the treatment of mild to moderate pain. Also acts on the hypothalamus heat-regulating center to reduce fever.
Adult Dose	650 mg PO bid/tid/qid; not to exceed 4 g/d in equally divided doses
Pediatric Dose	10-15 mg/kg/dose q4-6h; not to exceed 60-80 mg/kg/d
Contraindications	Documented hypersensitivity; liver damage; hypoprothrombinemia; vitamin K deficiency; bleeding disorders; asthma; children (<16 y) with flu (because of association with Reye syndrome)
Interactions	Effects may decrease with antacids and urinary alkalinizers; corticosteroids decrease salicylate serum levels; additive hypoprothrombinemic effects and increased bleeding time may occur with coadministration of anticoagulants; may antagonize uricosuric effects of probenecid and increase toxicity of phenytoin and valproic acid; doses >2 g/d may potentiate glucose-lowering effect of sulfonylurea drugs
Pregnancy	D - Unsafe in pregnancy
Precautions	May cause transient decrease in renal function and aggravate chronic kidney disease; avoid use in patients with severe anemia, with history of blood coagulation defects, or taking anticoagulants
Drug Name	Ibuprofen (Advil, Motrin, Nuprin) -- Usually the DOC for the treatment of mild to moderate pain, if no contraindications are present.
Adult Dose	200-400 mg q4-6h while symptoms persist; not to exceed 3.2 g/d
Pediatric Dose	30-70 mg/kg/d tid/qid
Contraindications	Documented hypersensitivity; peptic ulcer disease; recent GI bleeding or perforation; renal insufficiency; high risk of bleeding
Interactions	Coadministration with aspirin increases risk of inducing serious NSAID-related adverse effects; probenecid may increase concentrations and, possibly, toxicity of NSAIDs; may decrease effect of hydralazine, captopril, and beta-blockers; may decrease diuretic effects of furosemide and thiazides; monitor PT closely (instruct patients to watch for signs of bleeding); may increase risk of methotrexate toxicity; phenytoin levels may be increased when administered concurrently
Pregnancy	B - Usually safe but benefits must outweigh the risks.
	Category D in third trimester of pregnancy; caution in

Precautions	congestive heart failure, hypertension, and decreased renal and hepatic function; caution in anticoagulation abnormalities or during anticoagulant therapy

Drug Name	Acetaminophen (Tylenol, Aspirin Free Anacin, Feverall) -- DOC for treatment of pain in patients with documented hypersensitivity to aspirin, upper GI disease, or oral anticoagulants.
Adult Dose	325-650 mg q4-6h or 1000 mg tid/qid; not to exceed 4 g/d
Pediatric Dose	<12 years: 10-15 mg/kg/dose q4-6h prn; not to exceed 2.6 g/d >12 years: 325-650 mg q4h; not to exceed 5 doses in 24 h
Contraindications	Documented hypersensitivity; G-6-PD deficiency
Interactions	Rifampin can reduce analgesic effects of acetaminophen; coadministration with barbiturates, carbamazepine, hydantoins, and isoniazid may increase hepatotoxicity
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Hepatotoxicity possible in chronic alcoholics following various dose levels; severe or recurrent pain or high or continued fever may indicate serious illness; acetaminophen is contained in many OTC products and combined use with these products may result in cumulative acetaminophen doses exceeding recommended maximum dose

Drug Category: *Corticosteroids* -- Have anti-inflammatory properties and cause profound and varied metabolic effects. Corticosteroids modify the body's immune response to diverse stimuli. May shorten the course and reduce the pain of sunburn.

Drug Name	Prednisone (Deltasone, Orasone, Meticorten) -- May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.
Adult Dose	40-60 mg/d PO
Pediatric Dose	1 mg/kg PO qd
Contraindications	Documented hypersensitivity; viral infection, peptic ulcer disease, hepatic dysfunction, connective tissue infections, and fungal or tubercular skin infections; GI disease
Interactions	Coadministration with estrogens may decrease prednisone clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics
Pregnancy	B - Usually safe but benefits must outweigh the risks.
Precautions	Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use

FOLLOW-UP

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Further Inpatient Care:

- Inpatient care is indicated for severe burns, secondary infection, or control of severe pain.
- Indications for admission to a dedicated burn unit are the same as those for thermal burns.

Further Outpatient Care:

- Outpatient care is indicated for most cases of sunburn.
  - Cool baths or showers
  - Anti-inflammatory/analgesic medications
  - Avoidance of further sun exposure

In/Out Patient Meds:

- Topical anesthetic sprays or creams may cause sensitization and consequent dermatitis and, therefore, should be avoided.

Transfer:

- Only the most severe cases of sunburn, with marked involvement of a large percentage of the body surface area, require transfer to a burn unit for treatment.

Deterrence/Prevention:

- Prevention is the most effective therapy for sunburn. Individual and community educational programs can be effective in decreasing overall sun exposure or increasing use of sunscreen or protective clothing.
- Avoid sun exposure, especially during the period of peak solar radiation flux (from 10 am to 2 pm).
- Wear protective clothing, including hats or sun visors.
- Regularly use sunscreens with an adequate sun protection factor (SPF) for a given skin type (see Race).
  - SPF refers to the time needed to produce erythema on protected skin as a factor of the time to produce erythema on unprotected skin.
  - In general, use of a sunscreen with an SPF of 30 is sufficient.

- Apply at least 30 minutes prior to sun exposure and reapply often.
- Use waterproof sunscreens when swimming or perspiring heavily.
- Physical barriers (eg, zinc oxide, talc, titanium dioxide) provide excellent protection but are less appealing cosmetically.
- Chemical barriers are used in most sunscreens. Para-aminobenzoic acid (PABA) and PABA esters, which diffuse into stratum corneum and bind, are used most commonly, but they may stain clothing or produce contact dermatitis. Other chemical blocking agents include cinnamates, salicylates, anthranilates, and benzophenones. Many sunscreens employ a combination of agents.

Complications:

- Sunburns can exacerbate other skin diseases.
- Sunburns may trigger recurrence of herpes simplex, lupus, porphyria, or other cutaneous disorders.
- Sunburns may be associated with other heat-related illnesses, including dehydration, heat exhaustion, and heatstroke.
- Long-term exposure of the skin can lead to multiple deleterious effects, including premature aging and wrinkling of the skin (dermatoheliosis), development of premalignant lesions (solar keratoses), and development of malignant tumors (eg, basal cell carcinoma, squamous cell carcinoma, melanoma).
- Excessive exposure of the eyes to UVR can lead to discoloration of the lens and nuclear cataract formation.
- Photokeratoconjunctivitis, or snow blindness, may exist concurrently with sunburn.

Prognosis:

- Uncomplicated cases of sunburn resolve spontaneously over 4-7 days with scaling and desquamation but without acute sequelae.
- Long-term exposure to UVR is associated with several deleterious effects on the skin, as delineated above.

Patient Education:

- Short- and long-term complications (see Complications)
- Prevention (see Deterrence/Prevention)

Medical/Legal Pitfalls:

- Since window glass blocks UV-B, patients presenting with solar reactions occurring from exposure through window glass should be evaluated for phototoxic reactions and porphyria.
- Easy sunburning during infancy may indicate a serious underlying disease, such as porphyria or xeroderma pigmentosum. Referral for further evaluation is prudent.
- Obtain a complete drug exposure history in any patient with a rash.

Special Concerns:

- Avoid use of PABA and PABA esters on children younger than 6 months.

BIBLIOGRAPHY

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- Bickers DR: Sun-induced disorders. Emerg Med Clin North Am 1985 Nov; 3(4): 659-76 [Medline].
- Cavallo J, DeLeo VA: Sunburn. Dermatol Clin 1986 Apr; 4(2): 181-7[Medline].
- Dietrich AJ, Olson AL, Sox CH, et al: A community-based randomized trial encouraging sun protection for children. Pediatrics 1998 Dec; 102(6): E64[Medline].
- Green A, Williams G, Neale R, et al: Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial [published erratum appears in Lancet 1999 Sep 18;354 (9183):1038]. Lancet 1999 Aug 28; 354(9180): 723-9[Medline].
- Hall HI, McDavid K, Jorgensen CM, Kraft JM: Factors associated with sunburn in white children aged 6 months to 11 years. Am J Prev Med 2001 Jan; 20(1): 9-14[Medline].
- Kramer DA, Steinmark R: Sun-induced disorders. In: Schwartz GR, et al, eds. Principles and Practice of Emergency Medicine. 3rd ed. Philadelphia: Williams & Wilkins; 1992:2897-2904.
- Moehrle M, Koehle W, Dietz K, Lishka G: Reduction of minimal erythema dose by sweating. Photodermatol Photoimmunol Photomed 2000 Dec; 16(6): 260-2[Medline].
- Norris PG, Gange RW, Hawk JLM: Acute effects of ultraviolet radiation on the skin. In: Fitzpatrick TB, et al, eds. Dermatology in General Medicine. 4th ed. New York: McGraw-Hill; 1993:1651-8.
- Pathak MA, Fitzpatrick TB: Preventive treatment of sunburn, dermatoheliosis, and skin cancer with sun-protective agents. In: Fitzpatrick TB, et al, eds. Dermatology in General Medicine. 4th ed. New York: McGraw-Hill; 1993: 1689-98.
- Perpall A: Selected environmental skin disorders. Emerg Med Clin North Am 1992 May; 10(2): 437-48[Medline].
- Potts JF: Sunlight, sunburn, and sunscreens. Preventing and remedying problems from 'too much fun in the sun'. Postgrad Med 1990 Jun; 87(8): 52-5, 59-60, 63[Medline].

confirmed in the package insert. FULL DISCLAIMER

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Sunburn excerpt

Radiation Safety Answers

Answer to Question #13

Yale University has medical, veterinary, and research x-ray equipment. The specific types of x-ray equipment may be designed to image human patients, animals, viruses, ceramics, and for a large number of other purposes.

Yale has medical xray equipment used under the direction of a physician for diagnostic purposes. For example, the medical x-ray equipment located at the YHSC at 17 Hillhouse is surveyed and calibrated on a regular basis by physicists with the RSS. This equipment can only be operated by a trained person who is licensed with the State of CT Dept. of Environmental Protection.

All University owned x-ray equipment used for clinical reasons (ie. x-ray examinations on humans) is inspected by Radiation Safety to insure proper functioning. Shielding, personnel dosimetry requirements and safety procedures are handled by Radiation Safety. Only properly trained, certified personnel may expose humans using medical x-ray equipment.

Other x-ray equipment may include portables, C-arms, therapy units or diagnostic x-ray units. Use of such veterinary or cell irradiation x-ray equipment may also require shielding to protect persons in the surrounding area. Personnel dosimeters are generally required for personnel using veterinary x-ray equipment. Safe use of the equipment requires proper equipment use training. Safety procedures are supervised by Radiation Safety.

Radiation Safety should be notified as soon as any purchase of x-ray equipment is planned so that shielding and other safety requirements can be determined. X-ray equipment must be registered with the State of Connecticut Department of Environmental Protection. Any fees are the responsibility of the Principal Investigator.

For further information about State of Connecticut regulations and safe use of x-ray equipment, call Radiation Safety.

After appropriate training, persons at Yale may be permitted to use veterinary equipment for research projects that involve the x-raying of animals. These x-ray units are also surveyed for safety on a routine basis by members of the RSS.

X-ray diffraction units have very high dose rate x-ray beams. They can be used to image virus crystals and other materials. After appropriate, specific training, persons working at Yale may be allowed to use XRD units under the supervision of a Principal Investigator. [link to page 76 of manual]

The following information should be read by all users of x-ray diffraction units.

I. Hazards of Operating Machine Sources of X-Rays

The radiation from x-ray machines can be very dangerous, and such danger should not be minimized. On the other hand, there is no reason to be afraid to operate these machines after receiving proper training and instructions. The operator of an analytical x-ray machine should never become complacent or overconfident about the potential danger from an x-ray beam.

Numerous safety devices may be provided, but the user should not depend too heavily on these safety

devices lest he become overconfident. If a safety device should fail unnoticed, serious injury may result. Adequate safeguards must be provided, but these can never replace constant vigilance and alertness to possible danger. Proper training in the operation of these machines should teach the nature of the hazards so that the user can be properly alert and vigilant.

The wavelengths of the x-rays used most commonly in x-ray diffraction and fluorescent x-ray spectroscopy fall in the range from approximately 0.5 to 10A. These are so-called "soft" x-rays which are readily absorbed in matter. A thickness of only a few mm or less of Al, Fe, or Pb is required to reduce the intensity of the transmitted beam to 1/10 that of the initial intensity even for x-rays with a wavelength of 0.5A. The 1.54A wavelength corresponds to CuKa radiation, and 1.93A is the wavelength of FeKa radiation. These are commonly used sources in x-ray diffraction work.

It is apparent that only relatively thin layers of shielding are required to protect against this radiation, but it is this same property that makes these x-rays very dangerous. They are highly absorbed in soft tissue, and severe burns can result from exposure of the hands, arms, skin or eyes to the direct or diffracted beams. The maximum permissible dose of radiation for various parts of the body are shown in Table I. For comparison, x-ray intensities that may be obtained with high-power tubes and strongly diffracting crystals are also shown in Table I. It is apparent that a dose of 100 to 500 times the permissible yearly dose may be obtained from a 1-second exposure to the most intense direct beam. Even a strong diffracted beam can deliver the maximum permissible yearly dose to the eye in less than 10 minutes.

II. Biological Effects of Intense X-Ray Beams

It is possible to provide a general classification of the kind of changes that ionization radiation can produce in skin. It is useful to categorize these effects into three areas.

1. Reversible changes.

2. Conditional reversible changes.

3. Irreversible changes

A. Reversible Changes

The most common and earliest reversible change is the production of reddening of the skin or erythema. If the dose and energy is low enough that most of the radiation is absorbed in the superficial layers of the skin, reddening occurs, then disappears apparently with no future effects. Another reversible change is the loss of hair or epilation. It is possible to give a dose of radiation that will stop cell division in the epithelial cells so that hair ceases to grow temporarily and falls out. With a low dosage, the hair will begin to grow after a period of time, with no apparent permanent ill effects. A third system that shows reversible effects are the sebaceous glands (oil-producing glands in the skin) which are temporarily affected to produce less sebum (oil secretion of these glands in the skin).

B. Conditional Reversible Changes

Pigmentation of the skin is not a totally reversible change. If a large area of skin is irradiated, erythema and pigmentation will occur with the pigmentation eventually fading. It has been shown that the resulting skin is not normal and has some "memory of the injury." Future doses of the same area do not produce the same skin response.

C. Irreversible Changes

If enough radiation of the proper energy is absorbed in the skin this will result in permanent destruction of either hair or sweat glands, or whole skin, with a resulting scar. The irreversible changes are categorized in the heading of:

1. Radiation Dermatitis

2. Chronic radiation dermatitis

3. Radiation cancer

A summary of the various effects to be expected after given acute dose to low energy x-rays and the time of exposure to receive the dose in the beam are given in Table II on page 75.

Sources of Exposure

1. The primary beam.

2. Leakage of primary beam through cracks in shielding.

3. Penetration of primary beam through shutters, cameras, beam stops, etc.

4. Secondary emission (fluorescence) from a sample or shielding material.

5. Diffracted rays from crystal.

6. Radiation generated by rectifiers in the high voltage power supply.

TABLE 1

NRC OCCUPATIONAL EXPOSURE LIMITS*

YEARLY LIMIT (mrem)

WHOLE BODY 5000

SKIN OF THE WHOLE BODY 50000

EXTREMITY 50000

LENS OF EYE 15000

MINORS (PERSONS UNDER THE AGE OF 18) 500

FETAL EXPOSURE 500/Nine months

*Note: State of Connecticut exposure limits vary slightly. For more information contact Radiation Safety.

If you would like more information, or have additional questions, please contact Aggie Barlow, Radiation Safety Officer.